Ecology and industrial microbiology

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Editorial overview

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Although traditional industrial microbiology has been in practice for centuries, yielding interesting foods, drinks and condiments, a new era began early in the 20th century that featured the microbial production of several new products, such as organic acids, solvents, vitamins and enzymes. Bursting onto the scene in the middle of this century were the antibiotics and antitumor compounds, which were produced in large-scale fermenters and which revolutionized the practice of medicine. From the 1950s to the 1980s, new antibiotics and anticancer agents were rolled-out by the pharmaceutical industry, one after another, so that natural compounds or their derivatives represented half of the new pharmaceutical products being produced. Despite the advances in molecular biology since the 1950s, the development of recombinant DNA and the birth of the biotechnology business in the early 1970s, the discovery of new natural products useful in medicine has slowed down. At the same time, the total number of drugs submitted to the regulatory agencies, and the number of these drugs that are approved has dropped continuously, despite major increases in money spent on research and development. This is probably because of a number of events: the mega-mergers of the pharmaceutical industry, the major commitment of these companies to combinatorial chemistry and high-throughput screening, and the huge amounts of money spent on elucidation of the human and other genomes. Whatever the reason, it is clear that we must return to the search for natural products, but not in the same way; we must employ new techniques to find novel therapeutics, novel enzymes and we must modernize the methods of improving industrial microbial strains.

Today, another area of great importance is microbial ecology, especially involving the study of the diversity and functionality of microbial communities in natural and manmade environments, for instance in industrial-waste treatment reactors. Many microbes are able to live in biofilm communities; their use of chemical communication is fascinating and deserves considerable attention. Finally, a detailed understanding of the regulation of virulence and persistence of microbes of importance to bioterrorism appears crucial. Microbial ecology and industrial microbiology have come closer together in recent years as a result of the discovery that the vast number of microbial species (95–99.9%) has not yet been grown in the laboratory and that studies of biodiversity and biogeography offer the potential to lead us to discover new processes and novel natural products.

The vast abundance of as-yet undiscovered bioactive natural compounds will provide the drugs of the future, as well as new applications in agriculture and industry; of this there is no doubt. One very exciting source is the endophytic microbes living in the tissues of plants. Strobel has been working for many years on microbial diversity in the rainforests of the world, and

especially with plants in which these endophytic fungi and bacteria exist and thrive. He has discovered many novel compounds, but in his review here, he focuses on a single fungal genus, *Muscador*, and its ability to produce volatile organic bioactive compounds. These exciting compounds can inhibit many pathogenic fungi and bacteria, and synergistically are lethal. He discusses the discovery of this genus, the compounds produced, the physiology of their production and the new concept of ''mycofumigation''; commercial agricultural products based on this discovery are on their way.

Another relatively untapped source of new microorganisms and novel products is the marine environment. Indeed, the greatest biodiversity in the world is found in the oceans. Findings that new deep-sea microbes exist that are different from their terrestrial counterparts have sparked new enthusiasm in this search and discovery effort. New genera of filamentous bacteria (actinomycetes) have been identified, some of which require salt for growth. This has surprised many who thought that actinomycetes isolated from the marine environment merely represented re-growth of spores of terrestrial soil actinomycetes, washed into the sea. These marine actinomycetes include the new genera *Salinispora* and *Marinospora*, which mostly produce novel secondary metabolites. Lam leads us through this exciting development and its tremendous potential, discussing indigenous marine actinomycetes, their distribution, and their novel metabolites of potential industrial significance.

Another means of improving the drug discovery process is through microbial genomics. Understanding of the genetics and genomics of natural product synthesis has boomed in the last ten to twenty years and has provided much insight into the ways these interesting compounds are made by microorganisms. Clustering of the relevant genes and biosynthetic enzymes has allowed the discovery of many new derivatives of old compounds, and of novel compounds known as 'unnatural natural products'. This area of research, combinatorial biosynthesis, offers great hope for the future as long as production titres of the new compounds can be increased, and broad activity-testing is available. Increases in titres could possibly be brought about by cloning the gene clusters into hosts that are capable of higher levels of secondary metabolite synthesis. The cloning of environmental DNA (known as metagenomics) into known organisms has also yielded novel compounds. Genomics studies have shown us that there are many more clusters of secondary metabolism genes in a single microbial strain than are needed for synthesis of the few products known to be produced by that strain. Van Lanen and Shen cover these possibilities in a comprehensive way and describe important areas such as whole genome sequence mining, genome scanning, cultivation and metagenomics, heterologous expression and the discovery of novel chemistry.

Directed evolution of enzymes is an area of increasing interest in industrial circles. For exploring sequence space of enzymes and creating novel enzymes, a combination of directed evolution and computational design is discussed by Johannes and Zhao. They remind us that many steps in industrial synthetic chemistry are carried out by biocatalysts and that over 500 products from numerous industries involve biocatalysis. They focus on developments over the last two years. Directed evolution, unlike rational design, depends on mutation and selection, not on the relation between enzyme structure and function. It involves error-prone PCR, DNA shuffling, saturation mutagenesis and high-throughput screening. Not only can improved enzymes — improved in activity, stability, selectivity, solubility and optima for pH and temperature — be created, but pathways can be manipulated by metabolic engineering and directed evolution to yield novel secondary metabolites for the pharmaceutical, chemical and food industries.

Production of organic acids, amino acids and ethanol are the focus of Wendisch, Bott and Eikmanns review. They show us how metabolic engineering has been applied to create new recombinant strains of *Escherichia coli* and *Corynebacterium glutamicum* that are of interest to industry. These two species of bacteria have been studied for many years providing knowledge of their carbon metabolism and their physiology, thus allowing efficient application of metabolic engineering. The compounds of particular interest in this contribution are acetate, pyruvate, lactate, succinate, lysine, serine and ethanol.

Wastewater bioreactors contain microbial communities that are of a similar complexity to those in a variety of natural environments. Bramucci and Nagarajan review progress towards a better understanding of microbial communities in industrial wastewater bioreactors. As previously observed for natural environments, only a small portion of the population in wastewater bioreactors can be isolated and grown as pure microbial strains in the laboratory. Recent advances in molecular tools increasingly enable identification and characterization of the microbes in these bioreactors. The challenge now facing wastewater engineers and microbiologists is to relate microbial community analysis to the metabolic function of specific groups of bacteria within a wastewater bioreactor. The unique growth conditions in these bioreactors also facilitate formation of novel biochemical pathways through horizontal gene transfer and recruitment of different genes from diverse hosts into a single host. Thus, wastewater is a very promising source for new biocatalysts.

Marine microbial ecology is making striking advances; the marine environment has emerged as a prime resource for the isolation of novel organisms and novel chemistry in search and discovery. Ward and Bora review the diversity

and biogeography of marine actinobacteria. Very different views of actinobacterial diversity have emerged from cultivation and molecular approaches. Habitats in the marine environment are diverse, and vary greatly in geophysical characteristics. The biogeographic data for marine actinomycetes that has become available in recent years is discussed; this data are highly relevant with respect to practical implications, defining clear strategies for search and discovery, but also with major ecological and evolutionary implications.

Bacterial cell–cell communication by small signalling molecules has been intensively studied in the last decade. The first signalling molecules to be identified were the γ-butyrolactones from *Streptomyces*. These are fascinating compounds, which mainly regulate the production of antibiotics and cellular differentiation. Takano reviews new insights into their synthesis and degradation, and the molecular mechanism of the γ-butyrolactone regulatory system. These signal molecules are produced in a diversity of actinomycetes. Current evidence indicates that they are widespread regulators of antibiotic production in actinomycetes. The importance of understanding how secondary metabolites are regulated, and how environmental and physiological signals are sensed, highlights the relevance of studying this system.

The various reviews in this issue, written by specialists in their respective fields, provide very interesting reading, representing strong progress in knowledge and understanding of these fields and providing fundamental insights in the topics under study.